# Design, Synthesis, Spectroscopic Characterization, and Antifungal Evaluation of Novel 7H, 8H-6-(4-Bromophenyl)-3-(Substituted Phenyl)-s-Triazolo[4,3- b]-1,2,4-Triazines

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***Abstract*—The increasing incidence of invasive fungal infections and the rapid emergence of multidrug-resistant fungal pathogens have created an urgent need for the development of novel antifungal agents with improved efficacy and unique chemical scaffolds. Nitrogen-rich fused heterocyclic systems, particularly those incorporating 1,2,4-triazole and 1,2,4-triazine moieties, have attracted considerable interest in medicinal chemistry because of their structural diversity, metabolic stability, and broad spectrum of biological activities. In the present study, a series of novel 7H,8H-6-(4-bromophenyl)-3-(substituted phenyl)-s-triazolo[4,3-b]-1,2,4-triazines (IVa–g) were synthesized through the cyclocondensation of 3,4-diamino-5-(substituted phenyl)-1,2,4-triazoles with p-bromophenacyl bromide under reflux in anhydrous ethanol. The synthesized compounds were purified by recrystallization and comprehensively characterized using melting point determination, FT-IR spectroscopy, $_1$H NMR spectroscopy, mass spectrometry, and elemental analysis, which confirmed the successful formation of the fused triazolo-triazine framework. The target compounds were obtained in good to excellent yields (60–90%), demonstrating the efficiency and practicality of the synthetic protocol. Their in vitro antifungal activity was evaluated against *Aspergillus niger*, *Penicillium* spp., and *Cladosporium* spp. using the agar diffusion method at concentrations of 500 µg/mL and 1000 µg/mL. Biological screening revealed concentration-dependent antifungal activity, with the nature of the aromatic substituent exerting a significant influence on biological performance. Compounds bearing electron-donating substituents, particularly hydroxy and methoxy groups, exhibited enhanced antifungal activity, while derivatives containing electron-withdrawing substituents such as nitro and chloro groups showed markedly reduced or negligible activity. Among the synthesized derivatives, compound IVc demonstrated the broadest spectrum and highest antifungal potency against all tested fungal strains. These findings establish the fused s-triazolo[4,3-b]-1,2,4-triazine scaffold as a promising platform for antifungal drug discovery and provide valuable preliminary structure–activity relationship insights for the rational design of more potent antifungal agents.**

***Index Terms*—Triazolo[4,3-b]-1,2,4-triazines; Fused heterocycles; Antifungal activity; Spectroscopic characterization; Structure–activity relationship; Medicinal chemistry;**

## I. INTRODUCTION

Fungal infections represent a major global public health challenge, particularly among immunocompromised patients, transplant recipients, individuals undergoing cancer chemotherapy, and patients with chronic metabolic disorders [1,2]. Modern clinical reports indicate that invasive fungal diseases account for over 1.5 million deaths annually [3]. The rapid global emergence of multidrug-resistant fungal pathogens including *Candida auris*, *Aspergillus fumigatus*, and opportunistic filamentous species has significantly diminished the clinical efficacy of frontline therapeutics [4,5].

The available therapeutic arsenal for treating systemic fungal infections remains restricted compared to antibacterial chemotherapy [6]. Existing clinical agents fall primarily into four structural classes: azoles, echinocandins, polyenes, and allylamines [7]. Although azoles have served as the

mainstay of therapy for decades, their long-term clinical reliance has driven resistance through target-site mutations [8,9]. Medicinal chemists are therefore actively investigating novel heterocyclic architectures capable of 0Cumventing established resistance mechanisms while displaying high selectivity and low host toxicity [10,11].

Nitrogen-rich heterocyclic rings are privileged frameworks in drug discovery [12]. Among them, 1,2,4-triazoles exhibit a wide array of biological applications, including antimicrobial, antifungal, antiviral, anticancer, anti-inflammatory, and enzyme inhibitory properties [13,14]. The presence of triheteroatom coordination facilitates strong hydrogen-bonding interactions with biological targets, enhancing binding affinity and metabolic stability [15, 16]. Similarly, 1,2,4-triazines represent another privileged pharmacophore with extensive synthetic flexibility and therapeutic utility [17,18].

Recent medicinal chemistry research has focused on fused heterocyclic hybrid systems [19,20]. Condensing a triazole ring onto a triazine core reduces conformational flexibility, increases aromatic stabilization, and provides multiple hydrogen-bond acceptor sites, frequently enhancing binding affinity toward fungal enzymes involved in ergosterol biosynthesis and nucleic acid pathways [21, 22]. Furthermore, incorporating halogen atoms particularly bromine into aromatic motifs is a proven strategy for enhancing lipophilicity, membrane permeability, and target affinity via halogen bonding [23,24]. Conversely, alkoxy and hydroxy substituents modulate electron density and hydrogen-bonding potential, influencing pharmacokinetic and pharmacodynamic profiles [25, 26].

While individual triazole and triazine derivatives have been widely reported, comprehensive studies examining the synthesis, spectroscopic profile, electronic substitution effects, and biological performance of 7H,8H -triazolo[4,3-b]-1,2,4-triazines remain limited [27, 28]. This study presents the targeted synthesis of a novel series of 7H,8H-6-(4-bromophenyl)-3-(substituted phenyl)-s-triazolo[4,3-b]-1,2,4-triazines, complete spectroscopic characterization, preliminary antifungal evaluation against three filamentous fungi, and a structure–activity relationship (SAR) analysis.

## II. MATERIALS AND METHODS

*a. Chemicals and Reagents*:All chemicals, reagents, and solvents were of analytical-reagent grade and were used as received unless otherwise stated. Substituted benzaldehydes, semicarbazide hydrochloride, sodium acetate, bromine, hydrazine hydrate (99%), *p*-bromophenacyl bromide, sodium bicarbonate, ethanol, methanol, *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and chloroform were obtained from commercial suppliers, including Sigma-Aldrich, Merck, and Spectrochem.

Absolute ethanol was dried over molecular sieves before use in moisture-sensitive reactions. Reaction progress and product purity were monitored by thin-layer chromatography (TLC) using precoated silica-gel aluminium sheets. Spots were visualized under UV light (254 nm) and, where required, by exposure to iodine vapour.

b. *Instrumentation:* Melting points were determined in open capillary tubes using a Büchi digital melting-point apparatus and are reported uncorrected.

FT-IR spectra were recorded using a Bruker Vector-22 FT-IR spectrophotometer with KBr discs over the range 4000–400 $cm^{-1}$.

$^1H$ NMR spectra were recorded on a Bruker Avance DPX-200 MHz spectrometer using $CDCl_3$ or DMSO-$d_6$ as solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in δ (ppm).

Electron-impact mass spectra (EI-MS) were recorded on a JEOL JMS-D300 mass spectrometer at an ionization energy of 70 eV.

Elemental analyses were performed using a Carlo Erba 1106 elemental analyser. The observed elemental compositions were in close agreement with the calculated values.

Synthesis

The target compounds were synthesized through a four-step sequence involving the preparation of benzalsemicarbazones, oxidative cyclization to 2-amino-1,3,4-oxadiazoles, hydrazine-mediated transformation to 3,4-diamino-1,2,4-triazoles, and subsequent cyclization with *p*-bromophenacyl bromide.

a. Synthesis of Benzalsemicarbazones

The appropriate substituted benzaldehyde (0.05 mol) was dissolved in warm ethanol (20 mL) and added dropwise to a stirred aqueous solution (30 mL) containing semicarbazide hydrochloride (0.05 mol, 5.57 g) and sodium acetate (0.075 mol, 6.15 g). The reaction mixture was refluxed for 2 h and subsequently cooled to room temperature. The resulting crystalline solid was collected by suction filtration, washed thoroughly with cold distilled water to remove inorganic salts, dried under vacuum, and recrystallized from ethanol to afford the corresponding benzalsemicarbazones.

b. Synthesis of 2-Amino-5-(Substituted Phenyl)-1,3,4-oxadiazoles

The appropriate benzalsemicarbazone (0.02 mol) was suspended in glacial acetic acid (40 mL). A solution of bromine (0.02 mol) in glacial acetic acid (10 mL) was added slowly with continuous stirring. Anhydrous sodium acetate (0.03 mol, 2.46 g) was then added portionwise to neutralize the hydrogen bromide generated during the reaction and facilitate oxidative cyclization.

The reaction mixture was stirred at ambient temperature for 8 h and then poured onto crushed ice (200 g). The precipitated solid was collected by filtration, washed thoroughly with water until neutral, dried, and recrystallized from ethanol to afford the corresponding 2-amino-5-(substituted phenyl)-1,3,4-oxadiazoles .

c. Synthesis of 3,4-Diamino-5-(Substituted Phenyl)-1,2,4-triazoles

The appropriate 2-amino-1,3,4-oxadiazole (0.01 mol) and hydrazine hydrate (99%, 0.03 mol, 1.5 mL) were dissolved in absolute ethanol (30 mL). The reaction mixture was refluxed for 6 h. After cooling, the mixture was poured into ice-cold water (100 mL), and the resulting precipitate was collected by filtration, washed with water, dried, and recrystallized from ethanol to yield the corresponding 3,4-diamino-5-(substituted phenyl)-1,2,4-triazoles.

d. Synthesis of 7H,8H-6-(4-Bromophenyl)-3-(Substituted Phenyl)-*s*-triazolo[4,3-*b*]-1,2,4-triazines

Equimolar amounts (1.0 mmol each) of the appropriate 3,4-diamino-5-(substituted phenyl)-1,2,4-triazole and *p*-bromophenacyl bromide (1.0 mmol, 0.278 g) were combined in anhydrous ethanol (50 mL). The reaction mixture was refluxed under magnetic stirring for 6 h.

Reaction progress was monitored by TLC using chloroform/methanol (9:1, v/v) as the developing solvent. After completion of the reaction, the mixture was cooled to room temperature and neutralized with 5% aqueous sodium bicarbonate solution to pH 8.0–8.5. The resulting precipitate was collected by filtration, washed with water, dried, and recrystallized from ethanol. Less-soluble analogues were recrystallized from DMF/methanol mixtures to obtain the purified target triazolo-triazines.

Antifungal Activity

Antifungal activity was evaluated by the disk-diffusion method using Potato Dextrose Agar (PDA) against *Aspergillus niger*, *Penicillium* spp., and *Cladosporium* spp.

*Preparation of Fungal Inoculum*

Fungal cultures were maintained on PDA slants at 28 ± 2 °C. Spore suspensions were prepared in sterile 0.9% saline containing 0.01% Tween-80 and adjusted to approximately $10^6$ CFU/mL.

*Disk-Diffusion Assay*

The test compounds were dissolved in DMSO to obtain concentrations of 500 and 1000 µg/mL. Sterile paper discs (6 mm diameter) were impregnated with 20 µL of the respective test solutions, dried, and placed on inoculated PDA plates.

Fluconazole or ketoconazole (100 µg/disc) was used as the standard antifungal control, while DMSO served as the negative control.

*Incubation and Evaluation*

The inoculated plates were incubated at 28 ± 2 °C for 48–72 h. Antifungal activity was evaluated by measuring the diameter of the inhibition zones in millimetres. All experiments were performed in triplicate.

The percentage inhibition was calculated using the formula:

$$\text{Percentage inhibition} = \frac{D_c - D_t}{D_c} \times 100$$

Where ($D_t$) is the inhibition-zone diameter produced by the test compound and ($D_c$) is the inhibition-zone diameter of the control.

Proposed Reaction Mechanism

The formation of the fused 7H,8H-*s*-triazolo[4,3-*b*]-1,2,4-triazine derivatives from the corresponding 3,4-diamino-1,2,4-triazoles and *p*-bromophenacyl bromide is proposed to proceed through sequential nucleophilic substitution and intramolecular cyclization.

Initially, the carbonyl carbon of *p*-bromophenacyl bromide acts as the principal electrophilic centre. Nucleophilic attack by the more reactive exocyclic amino nitrogen of the diamino-1,2,4-triazole generates an addition intermediate. Subsequent dehydration affords an imine-type intermediate. Intramolecular nucleophilic displacement by the adjacent amino nitrogen at the bromomethyl carbon then results in ring closure through an $SN^2$-type process, with elimination of bromide ion and formation of the six-membered triazine ring. Neutralization with sodium bicarbonate facilitates proton transfer and affords the fused triazolo-triazine framework.

Physical and Spectroscopic Characterization

The FT-IR spectra of compounds IVa–g exhibited characteristic N–H stretching bands in the range 3210–3260 $cm^{-1}$ and C=N stretching bands at approximately 1625–1650 $cm^{-1}$. The disappearance of the primary amine bands observed in the corresponding precursors IIIa–g supports formation of the cyclized products. Heterocyclic C–N stretching bands occurred in the region 1440–1465 $cm^{-1}$, while C–Br absorptions were observed around 550–565 $cm^{-1}$. Substituent-specific absorptions included phenolic O–H, nitro, chloro, and ether functionalities.

The $^1H$ NMR spectra showed a characteristic singlet near δ 2.55–2.68 ppm attributable to the methylene group of the newly formed triazine ring. The N–H proton appeared as a broad singlet at approximately δ 5.35–5.70 ppm. Methoxy substituents appeared near δ 3.6–3.8 ppm, whereas aromatic protons occurred predominantly in the δ 6.8–8.4 ppm region.

EI-MS spectra displayed molecular-ion peaks consistent with the reported molecular masses. The characteristic $M/M^{+2}$ isotope pattern associated with bromine was observed in approximately a 1:1 intensity ratio.

## III. RESULTS AND DISCUSSION

The multi-step synthetic strategy produced target 7H,8H-6-(4-bromophenyl)-3-(substituted phenyl)-s-triazolo[4,3-b]-1,2,4-triazines efficiently. As summarized in Table 1, isolated yields ranged from 60% to 90%. The highest yield (90%) was achieved for compound (p-methoxyphenyl analogue), whereas compound (2,4-dichlorophenyl analogue) exhibited the lowest yield (60%). Steric hindrance and electron withdrawal from halogen substituents likely reduce the nucleophilicity of ring precursors during cyclization, contributing to reduced yields in highly halogenated derivatives. Sharp melting points and single TLC spots across all products confirmed purity following recrystallization.

Table 1: Physicochemical and Synthetic Data of Target Compounds (IVa–g)

| Compound | Substituted Phenyl Group (R) | Molecular Formula | Formula Weight (g/mol) | Yield (%) | Melting Point (∘C) | TLC Rf value |
|---|---|---|---|---|---|---|
| Iva | $-C_6H_5$ (Phenyl) | $C_{16}H_{12}N_5Br$ | 354.21 | 80 | 155–157 | 0.62 |
| IVb | 4-$OCH_3$–$C_6H_4$ | $C_{17}H_{14}N_5OBr$ | 384.23 | 90 | 220–225 | 0.58 |
| IVc | 3-$OCH_3$,4-OH–$C_6H_3$ | $C_{17}H_{14}N_5O_2Br$ | 400.23 | 70 | 210–212 | 0.45 |
| IVd | 3,4-$(OCH_3)_2C_6H_3$ | $C_{18}H_{16}N_5O_2Br$ | 414.26 | 85 | 235–240 | 0.52 |
| IVe | 2-Cl, 5-$NO_2$–$C_6H_3$ | $C_{16}H_{10}N_6O_2BrCl$ | 433.65 | 75 | 245–247 | 0.68 |
| IVf | 3-$OC_2H_5$,4-$OCH_3$–$C_6H_3$ | $C_{19}H_{18}N_5O_2Br$ | 428.29 | 70 | 160–161 | 0.55 |
| IVg | 2,4-$Cl_2$–$C_6H_3$ | $C_{16}H_{10}N_5BrCl_2$ | 423.10 | 60 | 199–200 | 0.71 |

Antifungal Activity Profile

The target compounds demonstrated variable antifungal activity against *Aspergillus niger*, *Penicillium* spp., and *Cladosporium* spp. at concentrations of 500mu g/mL and1000mu g/mL (Table 2).

*Key Biological Observations:*

1. High Potency Analogue: Unsubstituted phenyl derivative demonstrated strong, selective inhibition against *A. niger*, but was inactive against *Penicillium* spp. and *Cladosporium* spp.
2. Broadest Spectrum Lead: Compound containing both 4-hydroxy and 3-methoxy groups, exhibited the broadest spectrum of activity, inhibiting all three test pathogens in a concentration-dependent manner.
3. Moderate Antifungal Agents: Derivatives bearing methoxy or ethoxy groups demonstrated moderate activity against *A. niger*, but minimal inhibition against the other strains.
4. Inactive Analogue Systems: Derivatives containing strong electron-withdrawing or halogenated combinations (2 -Cl, 5-$NO_2$ and 2,4 -$Cl_2$ were completely inactive across all tested fungal strains under experimental conditions.

Table 2: Antifungal Screening Results of Target Compounds (IVa–g)

| R-Group | Phenyl | 4-$OCH_3$–Ph | 3-$OCH_3$,4-OH–Ph | 3,4-$(OCH_3)_2$–Ph | 2-Cl,5-$NO_2$–Ph | 3-OEt,4-OMe–Ph | 2,4-$Cl_2$–Ph |
|---|---|---|---|---|---|---|---|
| A. niger (500 µg/mL) | Moderate | Low | High | Low | Inactive | Low | Inactive |
| A. niger (1000 µg/mL) | High | Moderate | High | Moderate | Inactive | Moderate | Inactive |
| Penicillium spp. (1000 µg/mL) | Inactive | Inactive | Moderate | Inactive | Inactive | Inactive | Inactive |
| Cladosporium spp. (1000 µg/mL) | Inactive | Inactive | Moderate | Inactive | Inactive | Inactive | Inactive |
| Overall Antifungal Profile | Selective (*A. niger*) | Moderate | Broad-Spectrum Lead | Moderate | Inactive | Moderate | Inactive |

The observed experimental data highlights several clear structure–activity relationship trends:

- Role of Electron-Donating Groups (EDGs): The presence of electron-donating groups (-OH and - $OCH_3$) on the phenyl ring linked to the $C_3$ position of the triazole ring significantly enhances antifungal performance. Oxygenated substituents increase electron density across the heterocyclic system and provide supplemental hydrogen-bonding capabilities, which may facilitate interactions with fungal enzyme targets. The combination of a hydrogen-bond donor (-OH) and acceptor (-$OCH_3$) yielded the most potent profile.
- Impact of Electron-Withdrawing Groups (EWGs): Strong electron-withdrawing or halogen substitution (-$NO_2$, -Cl) negatively impacted antifungal activity under assay conditions. Electron depletion on the aromatic core may alter molecular charge distribution and reduce binding affinity for key fungal targets, as demonstrated by the complete lack of activity.
- Influence of the p -Bromophenyl Core: The 4-bromophenyl group attached at $C_6$ of the triazine core confers a degree of hydrophobic character necessary for fungal cell wall/membrane penetration. Halogen bonding via bromine may also aid target stabilization.
- Rigid Fused Pharmacophore: The fused triazolo[4,3-b]-1,2,4-triazine ring system presents a rigid platform that holds critical pharmacophoric elements in a defined spatial arrangement, minimizing entropy loss upon target binding.

## IV. CONCLUSION

A series of novel 7H,8H -6-(4-bromophenyl)-3-(substituted phenyl)- s-triazolo[4,3-b]-1,2,4-triazines were successfully synthesized via a multi-step

sequence in good to high isolated yields (60 – 90%). FT-IR, $^{1}$H NMR, EI-MS, and elemental analyses confirmed the structure of all synthesized compounds. Biological screening revealed structure-dependent antifungal activity. Derivatives containing electron-donating hydroxy and methoxy groups exhibited promising antifungal profiles, with compound displaying broad-spectrum activity against *A. niger*, *Penicillium* spp., and *Cladosporium* spp. Conversely, halogen and nitro substitution resulted in reduced activity. Overall, the fused triazolo-triazine system represents a promising template for developing new antifungal leads.

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